Inhibition of nitric oxide and prostaglandin E_2 production by pyrrolylated-chalcones : synthesis, biological activity, crystal structure analysis, and molecular docking studies

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ABSTRACT

In search of potent anti-inflammatory agents, twenty-four chalcone derivatives including seven new compounds (**13 – 17**, **21** and **23**) containing pyrrole moiety were designed, synthesized, and assessed for their nitric oxide (NO) and prostaglandin E_2 (PGE_2) suppression ability on IFN-γ/LPS-induced RAW 264.7 macrophage cells. Results showed that none of the synthesized compounds were PAINS-associated molecules, with 3-(2,5-dimethoxyphenyl)-1-(1*H*-pyrrol-2-yl)-prop-2-en-1-one (compound **16**) exhibiting remarkable inhibition activity towards PGE_2 and NO production with IC_{50} values of 0.5 ± 1.5 µM and 12.1 ± 1.5 µM, respectively. Physicochemical and ADMET studies showed that majority of the compounds obey to Lipinski's rule of five (RO5) having high blood brain barrier (BBB) penetration, human intestinal absorption (HIA), P-glycoprotein (PgP) inhibition and plasma binding protein (PPB) inhibition. The obtained atomic coordinates for the single-crystal XRD of **16** were then applied in a molecular docking simulation, and compound **16** was found to participate in a number of important binding interactions in the binding sites of ERK and mPGES-1. Based on these results, we have observed the potential of compound **16** as a new hit anti-inflammatory agent, and these findings could serve as a basis for further studies on its mechanism of action.

KEYWORDS

Anti-inflammatory agents; Pyrrolylated-chalcones; Atomic coordinates

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